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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/773,336	01/31/2001	Jose Pozuelo	POZ 2 0004-3	4263

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EXAMINER
CELSA, BENNETT M

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/18/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/773,336	Pozuelo, J.
Examiner	**Art Unit**
Bennett Celsa	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 16, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above, claim(s) *1-8 and 16-19* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *9-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

Applicant's response dated 5/16/03 in paper no. 8 is hereby acknowledged.

Status of the claims

Claims 1-19 are currently pending.

Claims 9-15 are under consideration to the extent of the elected invention.

Claims 1-8 and 16-19 are withdrawn from consideration as being directed to a nonelected invention.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

2. Applicant's election of Group III (claims 9-15 in part to treating narcotic addiction by administering AMPT and Haldol) in Paper No. 6 (dated 10/7/02) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. This application contains claims 1-8 and 16-19 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Outstanding Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 103

4. Claims 9-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pozuelo US Pat. No. 4,117,161 (9/78) and Pachter et al. US Pat. No. 3,819,635 (6/74) .

The present claims (e.g. claims 9-13 and 15) are directed to a method of treating narcotic addiction (e.g. addiction to heroin or cocaine or amphetamines or marijuana) by administering:

I. alpha-methyl-para tyrosine (AMPT) and

II. 4-[4-(p-chlorophenyl)-4-hydroxy-piperidino]-4'-fluorobuyrophenone (HALDOL or HALOPERIDOL).

Pozuelo teaches the use of AMPT to treat narcotic (e.g. morphine, marijuana etc.) and/or amphetamine addiction by treating the craving and withdrawal symptoms when a patient is deprived of such narcotics and/or amphetamines. Pozuelo further teaches AMPT amounts (e.g. see patent claims) within the presently claimed scope, while further teaching that the "[T]he exact amount to be utilized varies from person to person depending on the degree of addiction and is determined emperically". See e.g. col. 2, especially lines 19-30.

The Pozuelo reference differs from the presently claimed invention by failing to further utilize HALOPERIDOL.

However, Pachter et al. teach that "[I]t has been reported in the literature that ... HALOPERIDOL ... has found some experimental use in the alleviation of narcotic addiction withdrawal symptoms" and it is therefore preferred to combine HALOPERIDOL with narcotic

antagonists (such as the Pachter et al. Reference 14-Hydroxymorphinan derivatives which are analogous in structure to NALTREXONE: e.g. see formulas in col. 4; and Table 5 reference to "NALOXONE") in order to produce a product preventing narcotic abuse and providing supportive therapy in the absence of opiates. See Pachter et al. Col. 16, especially lines 2-15. The Pachter reference teaches HALOPERIDOL oral administration of 0.5-5 mg two or three times daily (e.g. see col. 16, lines 15-20).

To the extent that the Pachter reference dosage differs from the HALOPERIDOL dosage presently claimed, in combination with AMPT , it is noted that the exact amount of HALOPERIDOL to be utilized in a combined formulation would vary from person to person depending on the degree of addiction and is determined empirically (e.g. see Pozuelo at col. 2, especially lines 19-30) and thus optimum dosage would be obvious to determine by a medical practitioner.

Accordingly, one of ordinary skill in the art at the time of applicant's invention would have been motivated to administer Pozuelo's AMPT composition with Pachter's HALOPERIDOL composition, since both treat narcotic addiction (e.g. address narcotic withdrawal symptoms); and in order to obtain the combined additive effect of each of the drugs taken separately.

Courts have determined that it is indeed obvious to one of ordinary skill in the art to co-administer two (or more) pharmaceuticals, each of which is taught to have the same utility, when

they are individually known to have that utility, absent unexpected results. See e.g. *In re Kerhoven*, 626 F.2d 846,205 USPQ 1069 (CCPA 1980).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to formulate dually administer AMPT and HALOPERIDOL for treating narcotic addiction as presently claimed.

5. Claims 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pozuelo US Pat. No. 4,117,161 (9/78) and Pachter et al. US Pat. No. 3,819,635 (6/74) as applied to claims 9-13 and 15 above, and further in view of Gooberman et al. US Pat. No. 5,789,411 (8/98: filed 6/96 or earlier) and/or Archer US Pat. No. 5,760,044 (6/98: filed 5/96) .

The present claims (e.g. claims 9-13 and 15) are directed to a method of treating narcotic addiction (e.g. addiction to heroin or cocaine or amphetamines or marijuana) by administering:

I. alpha-methyl-para tyrosine (AMPT) and

II. 4-[4-(p-chlorophenyl)-4-hydroxy-piperidino]-4'-fluorobuyrophenone (HALDOL or HALOPERIDOL);

and optionally further including NALTREXONE (e.g claim 14).

The combined Pozuelo and Pachter patent reference teaching (discussed above and hereby incorporated by reference in its entirety) differs from the presently claimed invention (e.g claim 14) in failing to additionally administer NALTREXONE to treat narcotic addiction.

However, the Archer Patent teaches the administration of NALTREXONE or NALOXONE , separately, or in combination with a morphine derivative (e.g. see formula in

abstract) to treat cocaine and amphetamine dependency. See e.g. Archer at col. 12; patent claims 18 and 20.

Similarly, Gooberman et al. patent teach administering NALTREXONE for treating opioid (e.g heroin) withdrawal. See e.g. col. 5 and Examples (e.g. example 1); patent claims 7, 9, 15, 23,29).

Accordingly, one of ordinary skill in the art at the time of applicant's invention would have been motivated to administer NALTREXONE along with AMPT and HALOPERIDOL in order to further treat narcotic addiction (e.g. to address narcotic withdrawal symptoms) in order to obtain the combined additive effect of each of the drugs taken separately.

Courts have determined that it is indeed obvious to one of ordinary skill in the art to co-administer two (or more) pharmaceuticals, each of which is taught to have the same utility, when they are individually known to have that utility, absent unexpected results. See e.g. *In re Kerkhoven*, 626 F.2d 846,205 USPQ 1069 (CCPA 1980).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to additionally administer NALTREXONE along with AMPT and HALOPERIDOL for treating narcotic addiction as presently claimed.

Discussion

Applicant's arguments directed to the above-identified obviousness rejections (e.g. the patents drawn to Pozuelo, Pachter and further in view of Gooberman and/or Archer) were considered but deemed nonpersuasive for the following reasons.

Applicant first argues that the patents taken separately fail to teach the combined use of AMPT and Haloperidol as well as benefits derived therein (e.g. increased efficiency of treatment regimes etc.).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant further argues that "in none of these cited patents... is disclosed tyrosine-hydroxlase ... or any biochemical bases that would provide a basis or suggestion for the combination of AMPT and Haloperidol".

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this

case, as pointed out in the rejection, both the prior art and the knowledge generally available to one of ordinary skill in the art provide the requisite motivation to combine. For example, Pachter et al. teach that "[I]t has been reported in the literature that ... HALOPERIDOL ... has found some experimental use in the alleviation of narcotic addiction withdrawal symptoms" and it is therefore preferred to *combine HALOPERIDOL with narcotic antagonists* (such as the Pachter et al. Reference 14-Hydroxymorphinan derivatives which are analogous in structure to NALTREXONE: e.g. see formulas in col. 4; and Table 5 reference to "NALOXONE") in order to produce a product preventing narcotic abuse and providing supportive therapy in the absence of opiates. See Pachter et al. Col. 16, especially lines 2-15. . Additionally, it was pointed out in the rejection(s) above that one of ordinary skill in the art at the time of applicant's invention would have been motivated to administer NALTREXONE along with AMPT and HALOPERIDOL in order to further treat narcotic addiction (e.g. to address narcotic withdrawal symptoms) in order to obtain the combined additive effect of each of the drugs taken separately. See also citation teaching of *In re Kerhoven*, 626 F.2d 846,205 USPQ 1069 (CCPA 1980).

Additionally, it is noted that in response to applicant's argument that the combination would result in certain unrecognized benefits and/or mechanism , the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant further argues that following the '635 patent teaching would result in a motivation to combine Haloperidol with a specific class of narcotic antagonists (14-hydroxymorphinan) that are entirely different than AMPT; and similarly following the '161 patent one would use AMPT as the sole active ingredient. This argument is unconvincing since its misguided in the following respects.

First, applicant is arguing the '161 and '635 patent references separately when the rejection clearly requires the combined teaching of these patent references. Secondly, applicant is not addressing the '635 patent explicit teaching of combining Haloperidol with "narcotic antagonists" other than those mentioned in the '635 patent. See e.g. '635 patent col. 16 first full paragraph cited in the rejection(s) above.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). It is clear that the above-cited obviousness rejections take into account only knowledge which was one within the level of ordinary skill at the time the claimed invention was made and does not rely on impermissible hindsight reasoning as alleged by applicant.

Applicant argues that "[I]t is often the case that the combination of two pharmaceutical agents will not have the same effect upon a patient as the effects of the two agents independently... there will be detrimental side effects resulting from combining various pharmaceutical agents."

Applicant's argument is not persuasive since the cited prior art of record addresses the successful use of drugs (e.g. AMPT, Haloperidol, Naltrexone) to treat analogous conditions (e.g drug dependency withdrawal systems) so as to engender a "reasonable expectation of success" regarding their combined efficacy. It is noted that absolute certainty is not required for obviousness.

Applicant further argues that neither the Gooberman et al. nor the Archer patents teach (or suggest) the combined use of AMPT with Haloperidol ; nor remedy the deficiencies of the patents to Pozuelo and Pachter et al. Additionally, applicant argues that following Gooberman or Archer would require the concomitant use of additional ingredients with Naltrexone (e.g . an anesthetic in Gooberman; a benzazocine derivative in Archer), which is not recited in the combination of present claim 14. These arguments were not found convincing.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, the use of "comprising" language in present claim 14 would not exclude the presence of additionally unclaimed

ingredients (e.g. an anesthetic for sedation; or a benzazocine derivative) prior to (or concomitant with) administering an opioid antagonist (e.g. Naltrexone) . Additionally, applicant fails to consider the Gooberman et al. and/or Archer Patent reference teachings taken as a whole as pointed out in the above obviousness rejection; since the use of Naloxone as the bioactive ingredient for addressing drug withdrawal symptoms is taught by Gooberman et al. (E.g. see '411 patent col. 6); and similarly, as pointed out in the rejection above, the Archer Patent teaches the administration of NALTREXONE or NALOXONE , *separately,* or in combination with a morphine derivative (e.g. see formula in abstract) to treat cocaine and amphetamine dependency. See e.g. Archer at col. 12; patent claims 18 and 20.

Applicant further argues "unexpected advantages of treatment schedules using AMPT and Haloperidol as compared to administering AMPT alone"; citing specification pages 9-11 and reports 16-19 on specification pages 32-36 in support.

This argument was considered but deemed nonpersuasive for the following reasons.

The data presented on specification pages 16-19 fails to provide any indication regarding the treatment of patients having narcotic addictions; nor does this evidence support a showing of synergy (e.g. unexpectedly greater than additive effective of drugs administered separately) regarding the combined therapy; nor is there any evidence of the use of controls. Similarly, the case reports (reports 16-19) fail to provide adequate results (e.g. details) as to determine comparisons between the use of Haloperidol and AMPT separately verse the combined effect as to make a determination regarding unexpected results (e.g. synergy); nor do these case reports

indicate the presence or absence of control studies so as to demonstrate the reliabiltiy and reproducibility of unexpected results. Accordingly, the specification disclosure fails to establish the requisite unexpected results required to overcome prima facie obviousness. .

Accordingly, the above obviousness rejections are hereby maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)
July 15, 2003

BENNETT CELSA
PRIMARY EXAMINER